

Remarks

I. Support for Amendments

The foregoing amendments to the claims are fully supported in the specification as originally filed. Specifically, the amendments to claims 20 and 32 are supported in the specification at pages 22-23, and in Example 1 at pages 28-30. Accordingly, these amendments do not add new matter, and their entry is respectfully requested.

II. Status of the Claims

By the foregoing amendments, claims 41-43 have been cancelled without prejudice or disclaimer, and claims 20 and 32 have been amended. These amendments do not add new matter to the present application. Upon entry of these amendments, claims 1, 2, 6, 12, 16-20, 22, 25, 28, 29, 31 and 32 are pending in the application, with claim 1 being the sole independent claim.

III. Summary of the Office Action

In the Office Action dated October 11, 2000, the Examiner has made or maintained four rejections of the claims. Applicants respectfully offer the following remarks to overcome each of these rejections.

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IV. *The First Rejection Under 35 U.S.C. § 103(a) Is Traversed*

In the Office Action at page 2, section 2, the Examiner has rejected claims 1, 2, 6, 12, 16-20, 22, 25, 28, 29, 31 and 32 under 35 U.S.C. § 103(a) as being unpatentable over Burmer, U.S. Patent No. 5,726,022 (Doc. Ref. AH1, of record; hereinafter "Burmer").

Applicants respectfully traverse this rejection.

As an initial matter, Applicants note that the Examiner states that this rejection has been "maintained" and that a rejection of claims 41-43 over Burmer has been "withdrawn." See Office Action at page 2, final two lines. However, Applicants respectfully wish to point out that this rejection over Burmer was not made in the Office Action issued on May 11, 1999 (Paper No. 9), nor in the final Office Action issued on January 5, 2000 (Paper No. 12). Hence, Applicants respectfully assert that this rejection of claims 1, 2, 6, 12, 16-20, 22, 25, 28, 29, 31 and 32 over Burmer is a new, and not a maintained, rejection, and that no rejection of claims 41-43 over Burmer has previously been made and therefore cannot be "withdrawn." The Examiner is respectfully requested to clarify this matter on the record.

The invention as presently claimed is drawn to methods of producing nucleic acid molecules using primer-adapters that comprise one or more ligands and one or more cleavage sites. As the Examiner has acknowledged in the present Office Action, Burmer does not disclose using primer-adaptor molecules to produce a product nucleic acid molecule. Moreover, Applicants wish to remind the Examiner that, as was discussed with the Examiner in detail during the interview held on August 22, 2000, the adaptors of Burmer are *not* contained on primers used for synthesis of a nucleic acid molecule. Instead, Burmer describes *ligating* double-stranded adaptors to nucleic acid fragments. This approach is considerably different from the presently claimed methods, wherein the adaptors become a

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part of the product molecule by serving as primers from which the product molecule is extended by the action of the one or more polypeptides having polymerase activity and/or reverse transcriptase activity. Burmer therefore is seriously deficient as a primary reference upon which to base a *prima facie* case of obviousness of the presently claimed invention.

Perhaps recognizing these deficiencies of Burmer, the Examiner apparently contends that these deficiencies are cured by knowledge available to one of ordinary skill in the art (*see* Office Action at page 2, final four lines). However, this contention is in error, since it has not been supported with any objective evidence or sound scientific reasoning. "Rarely . . . will the skill in the art component operate to supply missing knowledge or prior art to reach an obviousness judgment . . . Skill in the art does not act as a bridge over gaps in substantive presentation of an obviousness case" *Al-Site Corpn. v. VSI International, Inc.*, 174 F.3d 1308, 1324 (Fed. Cir. 1999). Moreover, an obviousness conclusion must be based on *facts*, rather than on generalities (such as a general and/or unsupported statement of knowledge available in the art). *See In re Warner*, 379 F.2d 1011, 1017 (C.C.P.A. 1967), *cert. denied*, 389 U.S. 1057 (1968); *see also In re Freed*, 425 F.2d 785, 788 (C.C.P.A. 1970). Since the Examiner has drawn the conclusion that an artisan of ordinary skill would have made a primer-adaptor such as that used in the presently claimed methods based on Burmer, but has pointed to no suggestion in Burmer nor any other objective evidence or sound scientific reasoning for reaching this conclusion, this contention cannot be supported in fact or in law.

From the context of this rejection, the Examiner appears to view the information that is explicitly missing from Burmer as inherent in that reference, or at least as within the level of ordinary skill in the art. Applicants wish to remind the Examiner, however, that there is

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no such thing as "inherent obviousness," since inherence and obviousness are different legal concepts. *See In re Spormann*, 150 USPQ 449, 452 (C.C.P.A. 1966). That which is inherent cannot be obvious, since inherent information "is not necessarily known [and] Obviousness cannot be predicated on what is unknown." *Id.* Since the present rejection is based on obviousness, any contention by the Examiner that is based on the possible presence of inherent knowledge in Burmer, or within the level of ordinary skill in the art, must necessarily fail.

Thus, Applicants respectfully assert that a *prima facie* case of obviousness of the presently claimed invention cannot be properly based on the disclosure of Burmer. Reconsideration and withdrawal of this rejection therefore are respectfully requested.

V. *The Second Rejection Under 35 U.S.C. § 103(a) Is Traversed*

In the Office Action at pages 3-5, the Examiner has maintained the rejection of claims 1, 2, 6, 12, 16-20, 22, 25, 28, 29, 31 and 32 under 35 U.S.C. § 103(a) as being unpatentable over Burmer in view of Carninci *et al.*, *Genomics* 37:327-336 (1996) (Doc. Ref. AR1, of record; hereinafter "Carninci"). Applicants respectfully traverse this rejection, and reiterate and incorporate by reference herein the remarks in traversal of this rejection that were included in Applicants' Amendment and Reply Under 37 C.F.R. § 1.111 filed on October 12, 1999, and in Applicants' Preliminary Remarks filed on August 28, 2000. In particular, Applicants wish to point out that, as noted above, the adaptors of Burmer are *not* contained on primers used for synthesis of a nucleic acid molecule. Instead, Burmer describes *ligating* double-stranded adaptors to nucleic acid fragments. Moreover, as was discussed with the Examiner during the above-referenced interview, the methods disclosed

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in Burmer will not permit addition of adapters to nucleic acid molecules without first digesting the nucleic acid molecules such that the adapter-containing fragments can be ligated to them. In contrast, adapters are added to nucleic acid molecules in the presently claimed methods by providing the adapters on *primer* molecules which serve as the starting point for the synthesis of new nucleic acid molecules comprising such adapters -- the adapters are *not* ligated directly to digested nucleic acid molecules in the present methods. Burmer therefore is seriously deficient as a primary reference upon which to base a *prima facie* case of obviousness of the presently claimed invention.

The deficiencies of Burmer are not cured by the disclosure of Carninci, for reasons discussed in detail in Applicants' reply of October 12, 1999. Specifically, and as the Examiner has stated, Carninci relates to the use of primers having restriction sites. However, there is no disclosure or suggestion in Carninci that primers containing both cleavage sites *and* ligands should be used in the methods described in Carninci. In fact, the only disclosure of the use of ligands in Carninci is for the labeling of cap structures on eukaryotic mRNA, which simply permits the capture of mRNA molecules to facilitate subsequent production of full-length cDNA. See Carninci in the Abstract; at page 328, column 2 through page 329, column 1; and in Figure 1 at page 330. There is no disclosure in Carninci that would lead one of ordinary skill in the art to use a primer-adaptor molecule containing both a ligand and a cleavage site for synthesis of a first nucleic acid molecule comprising the primer adaptor (and thus comprising the ligand and cleavage site). Thus, Carninci provides no disclosure or suggestion that would cure the above-noted deficiencies of Burmer.

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In proceedings before the Patent and Trademark Office, the examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki*, 223 USPQ 785, 787-88 (Fed. Cir. 1984). The Examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references in such a way as to produce the invention as claimed. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). Specifically, there must be a reason, suggestion, or motivation in the cited art that would motivate one of ordinary skill to combine the references, and that would also suggest a reasonable likelihood of success in making or using the invention as claimed as a result of that combination. *See In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). Absent such suggestion, motivation, and reasonable expectation of success, the cited references may not be properly combined to render the claimed invention obvious. *See Fine* at 1598. As discussed above, Burmer and Carninci, alone or in combination, do not disclose or suggest the presently claimed invention. Equally importantly, neither of the cited references contains any suggestion that its disclosure should be modified with any portion of the disclosure of the other reference in order to enable one of ordinary skill to have a reasonable expectation of success in making and using the claimed invention, without which the disclosures of these references may not be properly combined under *Fine* and *Dow*. Indeed, the Carninci reference was already available in the art (having been published in 1996) as of the filing date of the Burmer nonprovisional application (January 9, 1997), and even Burmer did not choose to use the primers of Carninci. Thus, the ordinarily skilled artisan would not have been motivated to combine the disclosures of Burmer and Carninci to make and use the claimed

invention with any reasonable expectation of success. The Examiner therefore has not met the burden required to sustain a *prima facie* case of obviousness.

In view of the foregoing remarks, Applicants respectfully assert that a *prima facie* case of obviousness of the claimed invention cannot be established based on the disclosures of Burmer and Carninci. Reconsideration and withdrawal of the rejection of claims 1, 2, 6, 12, 16-20, 22, 25, 28, 29, 31 and 32 under 35 U.S.C. § 103(a) are therefore respectfully requested.

VI. The Rejection Under 35 U.S.C. § 102(e) Over Burmer Is Traversed

In the Office Action at pages 5-6, sections 4-5, the Examiner has rejected claims 41-43 under 35 U.S.C. § 102(e) as being anticipated by Burmer. By the foregoing amendments, claims 41-43 have been cancelled. Thus, this rejection has been rendered moot.

VII. The Rejection Under 35 U.S.C. § 112, Second Paragraph, Are Traversed

In the Office Action at page 6, sections 6-7, the Examiner has rejected claims 6, 20 and 32 under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness. Applicants respectfully traverse this rejection.

A. The Rejection of Claim 6

In making this rejection the Examiner first contends that the use of “mutants and variants thereof” in claim 6 renders this claim indefinite because it is allegedly unclear what the metes and bounds of this term are. Applicants respectfully disagree. As currently presented, the term “mutants and variants thereof” is modified by the phrase “that are

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substantially reduced in RNase H activity.” Hence, as one of ordinary skill would appreciate, the metes and bounds of the “mutants and variants” recited in claim 6 are defined in *functional* terms -- *i.e.*, any mutant or variant that is substantially reduced in RNase H activity relative to the wildtype forms of the enzymes recited in the Markush group in this claim would be encompassed within the claimed invention. Thus, the meaning of the term “mutants and variants thereof” in claim 6 must be evaluated in the context in which it currently appears -- *i.e.*, in terms of the functional definition also used in this claim.

To this end, the Examiner has also questioned the meaning of the term “substantially reduced in RNase H activity,” asserting that the use of this term in claim 6 also renders this claim indefinite. Applicants respectfully disagree. The present specification provides a full and complete definition of what is meant by this term:

By an enzyme "substantially reduced in RNase H activity" is meant that the enzyme has less than about 20%, more preferably less than about 15%, 10% or 5%, and most preferably less than about 2%, of the RNase H activity of a wildtype or "RNase H⁺" enzyme such as wildtype M-MLV or AMV reverse transcriptases. The RNase H activity of any enzyme may be determined by a variety of assays, such as those described, for example, in U.S. Patent No. 5,244,797, in Kotewicz, M.L., *et al.*, *Nucl. Acids Res.* 16:265 (1988) and in Gerard, G.F., *et al.*, *FOCUS* 14(5):91 (1992), the disclosures of all of which are fully incorporated herein by reference.

Specification at page 16, line 25, to page 17, line 4. Thus, the term “substantially reduced in RNase H activity” as used in claim 6 is fully defined in the specification as originally filed.

As the Board has held:

[35 U.S.C. § 112, second paragraph] merely requires that the claims set forth and circumscribe a particular area with a reasonable degree of precision and particularity. The definiteness of the claim language employed must not be analyzed in a

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vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one having ordinary skill in the pertinent art.

Ex parte Moelands, 3 USPQ2d 1474, 1476 (Bd. Pat. App. Int. 1987) (citing *In re Moore*, 439 F.2d 1232 (CCPA 1971)). Since the present specification provides a definition of the term “substantially reduced in RNase H activity,” and assays (or at least, references thereto which are incorporated by reference into the present specification) to allow a determination of whether a given enzyme is “substantially reduced in RNase H activity,” one of ordinary skill could readily determine whether a mutant or variant polymerase fell within the metes and bounds of claim 6 as currently presented. Claim 6 thus comports with the requirements of 35 U.S.C. § 112, second paragraph, as interpreted under *Moelands* and *Moore*; reconsideration and withdrawal of this portion of the rejection therefore are respectfully requested.

B. The Rejection of Claims 20 and 32

The Examiner next contends that claims 20 and 32 are indefinite because it is allegedly unclear how the nucleic acid is isolated by cleavage of one or more cleavage sites. By the foregoing amendments, claims 20 and 32 have been amended to indicate that the cleavage acts to release the nucleic acid from the ligand-hapten complex to which it is bound. As noted above, the specification contains an ample description of one non-limiting example of this method of isolation (*see, e.g.*, specification at pages 22-23, in Example 1 at pages 28-30, and in Figure 1). Hence, one of ordinary skill would readily understand how the cleavage process recited in claims 20 and 32 participates in isolation of the nucleic acid, when these claims are read in view of the present specification (as they must be under

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Moelands and *Moore*). Claims 20 and 32 thus comport with the requirements of 35 U.S.C. § 112, second paragraph; reconsideration and withdrawal of this portion of the rejection therefore are respectfully requested.

VIII. Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn.

Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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Date: March 12, 2001

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Version with markings to show changes made

20. (Once amended) The method of claim 18 or claim 19, said method further comprising isolating said nucleic acid molecule from said complex by cleavage of one or more of said cleavage [sites.] sites, thereby releasing said nucleic acid molecule from said complex.

32. (Once amended) The method of claim 31, wherein said method further comprises isolating said nucleic acid from said complex by cleaving one or more of said cleavage [sites.] sites, thereby releasing said nucleic acid from said complex.

Claims 41-43 are cancelled.

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